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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,183	11/14/2001	Alan Gewirtz	43826-9	6995

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EXAMINER	
LACOURCIERE, KAREN A	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 02/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/993,183	GEWIRTZ, ALAN	
	Examiner	Art Unit	
	Karen A. Lacourciere	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *12 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I in the paper filed 10-14-2003 is acknowledged.

Claims 12 and 13 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the paper filed 10-14-2003.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Information Disclosure Statement

Reference number 36 on PTO form 1449, filed April 21, 2003 was not considered because the reference was not provided.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 7 and 8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-3, 7 and 8 provide for the use of RNA interference to achieve post-transcriptional gee silencing, but, since the claims do not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced. Claims 1-3, 7 and 8 do not provide any active method steps, but only specify "using RNA interference".

Claims 1-3, 7 and 8 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claims 4-6 and 9-11 are dependent on claim 1, but are not subject to the same grounds of rejection, as set forth above, because these methods do include additional steps, which provide active method steps for the claimed methods, but are indefinite for other reasons, as set forth below.

Claims 4-6, 9-11 and 14-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4-6, 9-11 are indefinite because the methods include unspecified or unclear method steps, as the base method in the parent claim does not actually provide any method steps. Claims 4-6 and 9-11 depend from claim 1, which describes a method comprising "using RNA interference". Each of claims 4-6 and 9-11 are drawn to methods wherein the methods comprise further steps, however, since the base method does not delineate any positive method steps, it is unclear what steps, in addition to the positive steps specified in claims 4-6 and 9-11, are comprised in the claimed methods.

Claim 4 recites the limitation "the target gene encoding the disrupted expression" in line three of the claim. There is insufficient antecedent basis for this limitation in the claim, because it depends from claim 1, which does not include a target gene. Claims 5, 6, 9, 10 and 11 are indefinite for the same reasons due to dependence on claim 4.

Claim 5 is indefinite because it is unclear what further step is being specified in the claim limitations. Claim 5 recites blocking mammalian gene function of the target gene encoding the disrupted expression, but the disrupted expression is actually target cell expression. Target cells are not encoded by a gene and it is unclear what is actually being blocked, if additionally agents provide the blocking, or if the claim is meant to further describe the actions of the dsRNA administered in the parent claim 4.

Claims 6, 9, 10 and 11 are indefinite because it is unclear how the method steps added in the dependent claims are related to the methods specified in the parent

claims. In each of claim 6, 9 and 11 the claimed methods recite the methods of the parent claims wherein the method further comprises steps that do not seem related to the parent claims. For example, in claim 6, the method further comprises screening dsRNA's and identifying the dsRNA, wherein in the method of the parent claim 4, a gene specific dsRNA has been administered, it is unclear if this is the same dsRNA, or if there is an antecedent basis problem, or how the screening method relates to the administered dsRNA, for example, how an unknown dsRNA can be administered in a gene specific manner, or if the method of claim 6 is an entirely separate method. In claim 9, the methods further comprise producing RNA based drugs. It is unclear if these RNA based drugs are produced in the disrupted target cell, or related to the dsRNA administered to the target cell, or if the production of the RNA-based drugs is a totally separate method. Similarly, in claim 10, it is unclear how the knockout model animal is related to the method of disruption. For example, is the disrupted cell used in the method of making the knockout animal, is the same dsRNA molecule used in the making of the knockout animal, or is the knockout animal even related to the method of disrupting target cell expression, or a totally separate method.

Claim 11 recites the limitation "the RNA-based drugs" in line one of the claim. There is insufficient antecedent basis for this limitation in the claim.

Claims 1-11 and 14-20 are indefinite due to the recitation of disrupting target cell expression at the mRNA level. It is unclear what this means, because target cells are not expressed by mRNA, but rather target cells themselves express mRNA. It is

unclear how expression of a cell is disrupted, for example, does this refer to cell proliferation, for example?

Claims 14-20 are indefinite because it is unclear whether the claimed methods require the administration of dsRNA, which mediates the RNAi, or if further method steps are part of the claimed methods, since the methods specify a method comprising "using RNA interference", which does not actually specify any active method step (see line 3 of claim 14).

Claims 1-11 are so unclear as to be meaningless, particularly due to the fact that the base claim, claim 1, does not provide any active method steps, that no prior art could reasonably be applied and enablement can not be assesed and, therefore, claims 1-11 have not been further examined on the merits.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 14-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 14-20 are directed to a method of treating a mammalian subject with an RNA based disorder or disease by administering a dsRNA preparation to post transcriptionally silence genes by RNA interference, including wherein the silencing occurs in a gene specific manner, is performed in a human subject, and in a malignant tumor cell.

The following factors have been considered in formulating this rejection (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988)): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

Claims 14-20 are drawn broadly to treating generally any RNA-based disease or disorder in a mammal using a dsRNA that initiates RNA interference. The specification provides an example wherein one gene target, KitR, is variably inhibited using a long (8282 bp) dsRNA in two different cells in culture. There are no examples wherein dsRNA is used to initiate RNA interference in any cells in a mammal in vivo, nor wherein dsRNA is used to initiate RNA interference and a therapeutic outcome is achieved for any RNA based disease or disorder in a mammal.

At the time the instant Application was filed, and even to date, nucleic acid based therapies were highly unpredictable. The filed of RNA interference was in its infancy and gene specific dsRNA inhibition in mammalian cells was also highly unpredictable, even in cells in culture and the ability to inhibit gene expression was variable and

unpredictable among different cells lines and different target genes. In particular, in mammalian cells, longer dsRNA molecules were observed to cause the induction of the PKR response, resulting in cell apoptosis and non-specific mRNA expression inhibition. Examples in the literature demonstrate that in some organisms, including zebrafish and mice, the inhibition by double stranded RNA was unpredictable or transient (see for example Oates et al. or Wianny et al. Attempts to 'knock out' gene function in an organism using double stranded RNA administered at the embryonic stage have demonstrated that inhibition by double stranded RNA is transient, and function is regained after multiple cell divisions (see for example Wianny et al.). Further, mammals, including humans, have demonstrated an immune response triggered by even small amounts of double stranded RNA that would preclude the use of double stranded RNA in vivo(whole organism) and in Xenopus an endogenous dsRAD activity would predict that dsRNA methods would not be effective (see for example Wianny et al. page 74).

After the filing date of this Application, the filed of RNA interference determined that shorter dsRNA molecules could overcome this PKR response, and resulted in a more predictable inhibitory response, however, guidance for the use of shorter dsRNAs, as discussed in the literature as necessary to predictably apply the claimed methods, was not provided in the instant specification. Even with the advances made by the filed of RNA interference, however, to induce inhibition by RNA interference in mammalian cells in culture, RNA interference is still recognized in the art as not enabled for therapeutic purposes. (See for example, Caplen et al., Coburn et al. and Agami et al.

for a review on the progression of RNA interference in mammalian cells and the state of the art of RNA interference for therapeutic purposes.) Caplen et al. points out that, even post filing in 2003, "Many of the problems associated with developing RNAi as an effective therapeutic as the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system". Coburn et al. also points out that the major impediment to using RNA interference as a therapeutic is that gene expression is transient and the delivery methods used for RNAi are not effective for therapeutic purposes (see for example p 754, first column, last paragraph). The filed of RNA interference is optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant Application, the filed recognizes that therapeutic methods are not yet effective.

RNA interference methods for therapeutic methods encounter the same problems long recognized in other nucleic acid based therapies, particularly with regard to the inability to specifically delivery an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a therapeutic effect. The problems of nucleic acid based therapies are well known in the art. For example, at the time the instant invention was made, the therapeutic use of nucleic acids was a highly unpredictable art due to obstacles that continue to hinder the therapeutic application of nucleic acids *in vivo* (whole organism) (see for example Agrawal et al. (Molecular Medicine Today, Vol 6, p 72-81, February 2000), Branch

(TIBS 23, Feb 1998, p45-50), Green et al. (J. Am Coll. Surg., Vol 191, No. 1, July 2000, p 93-105), Jen et al. (Stem Cells 2000, Vol. 18, p 307-319)). Such obstacles include, for example, problems with delivery, target accessibility and the potential for unpredictable nonspecific effects. These references discuss the problems of nucleic acid based therapies in reference to antisense and gene therapy methods, however, as pointed out in Caplen et al., RNA interference encounters similar problems as other nucleic acid based therapies.

Jen et al. state (see page 313, second column, second paragraph) "One of the major limitations for the therapeutic use of AS-ODNs and ribozymes is the problem of delivery....Presently, some success has been achieved in tissue culture, but efficient delivery for *in vivo* animal studies remains questionable". Jen et al. outlines many of the factors limiting the application of antisense for therapeutic purposes and concludes (see p 315, second column), "Given the state of the art, it is perhaps not surprising that effective and efficient clinical translation of the antisense strategy has proven elusive."

Green et al. state, "It is clear that the evolution of antisense technology from a laboratory research tool into a mechanism for designing active and effective drugs is far from complete. Although there is little doubt that systemically administered antisense ODNs can inhibit the expression of specific genes in patients, the effectiveness of such therapy in modifying the course of a particular illness has not yet been established....Clearly, additional work must be done to unravel the complex problems associated with drug delivery, mRNA targeting and aptameric, nonantisense effects."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo*, with a resultant therapeutic outcome, as claimed. The specification provides examples wherein a long dsRNA is delivered to two difference cell lines *in vitro* and the expression of kitR is variably inhibited, however, cell culture examples are generally not predictive of *in vivo* inhibition and the methods of deleivery of the two exemplified cell lines would not be applicable to delivery of dsRNA to a mammal. Often formulations and techniques for delivery *in vitro* (cell culture) are not applicable *in vivo* (whole organism) (see for example Jen et al., page 313, second column, second paragraph). For example, Agrawal et al. (see p 79-80, section entitled *Cellular uptake facilitators for in vitro studies*) states "The cellular uptake of negatively charged oligonucleotides is one of the important factors in determining the efficacy of antisense oligonucleotides.....In vitro, cellular uptake of antisense oligonucleotides depends on many factors, including cell type, kinetics of uptake, tissue culture conditions, and chemical nature, length and sequence of the oligonucleotide. Any one of these factors can influence the biological activity of an antisense oligonucleotide." Agrawal discusses these factors in relation to antisense, but would also apply to dsRAn. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results.

The specification does not provide the guidance required to overcome the art recognized unpredictability of dsRNA for use in RNA interference in mammalian cells and in the therapeutic application of RNAi in a mammal. The field of RNA interference

does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods. Therefore, the skilled artisan would not have been able to practice the broadly claimed methods of treating a mammal without undue, trial an error experimentation and, therefore, claims 14-20 are not enabled.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Lacourciere whose telephone number is (703) 308-7523. The examiner can normally be reached on Monday-Thursday 7:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Karen A. Lacourciere
January 11, 2004

KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER